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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 08/368,776 | 01/03/95 | CIOSSEK T | |

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HM12/0929

| EXAMINER | |
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| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | 32 |

DATE MAILED: 09/29/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 08/368,776 | Ciosseck et al |
| **Examiner** | **Group Art Unit** |
| Ungar | 1642 |

☒ Responsive to communication(s) filed on *Jul 7, 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1, 3, 4, 16, 18, 19, 21, 22, 24, and 25* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *3, 4, and 24* is/are allowed.

☒ Claim(s) *1, 16, 18, 19, 21, 22, and 25* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

1. The Amendment filed April 24, 2000 (Paper No. 30) and the Amendment filed July 7, 2000 (Paper No. 31) in response to the Office Action of December 13, 2000 (Paper No. 28) are acknowledged and have been entered. Previously pending claims 2 and 17 have been canceled, claims 1, 3, 4, 16, 18, 19, 21, 22, 24 and 26 have been amended. Claims 1, 3-4, 16, 18-19, 21-22 and 24-26 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following objections are being maintained.

Objection to the specification in Paper No. 28 page 3 is maintained.

Applicant argues that amendment of the specification to provide explicit sequence identification numbers within the Brief Description of the Drawings overcomes the objection. The argument has been considered but has not been found persuasive because Applicant has not clarified the differences between the submitted sequences and those shown in the figures as originally filed.

***New Grounds of Rejection***

***Claim Rejections - 35 USC § 101***

4. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

5. Claims 18 and 19 as drawn to polynucleotides encoding SEQ ID Nos 3 and 5 or nucleic acids encoding said sequences, claim 25 as drawn to all combinations other than sequences encoding amino acids 580-998 of SEQ ID NO:2 or their complete complement, claim 26 as drawn to claims 19, 22, 24 and 25 and claims 21, 22, are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The disclosed utilities for the claimed nucleic acids include methods for treatment, diagnosis and screening for diseases or conditions characterized by an abnormality in a signal transduction disorder wherein the signal transduction pathway involves an interaction between a MDK1 receptor tyrosine kinase and a receptor for the kinase (see abstract). However, neither the specification nor any art of record teaches what the claimed sequences which do not encode tyrosine kinases domainsare, what they do, they do not teach a utility for any of the fragments claimed, do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases. Additional asserted utilities for the claimed sequences, such as production of and screening of agonists, antibodies and antagonists apply to many unrelated polynucleotide sequences. Therefore the asserted utilities are not considered "specific" utilities, i.e. they are not specific to the claimed sequences. Additional disclosed utilities for the claimed sequences include therapy and diagnosis and screening for diseases or conditions characterized by an abnormality in a signal transduction disorder wherein the signal transduction pathway involves an interaction between a MDK1 receptor tyrosine kinase and a receptor for

the kinase, however, none of these sequences or fragments comprise a MDK1 receptor tyrosine kinase domain. Further, the specification, speculates that the truncated versions of MDK1 might have a variety of functions based on a number of truncated receptor domains with some homology to the claimed truncated sequences, some of which are secreted, some of which are still anchored to cell membranes and which are expressed in a variety of tissues. However, it is not possible to determine from the information in the specification what the truncated moieties or fragments are or what they do. The specification does not teach a utility for any of the fragments claimed, do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases. The specification, however, makes clear that the sequences of the reported truncated receptors and fragments are different than those of the claimed sequences. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three

dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al ( J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, since the claimed sequences are different than the cited moieties it could not be predicted, nor would it be expected that their function would be the same as the function of the cited moieties. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular

and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399 para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al, Lazar et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with the clearly indicated dissimilarities it could not be predicted, based on similarity with the cited molecules, nor would it be expected that the function of the claimed sequences would be the

same as that of cited molecules. Further, even if the claimed sequences were related to the cited molecules, neither the specification nor any art of record teaches what the polynucleotide is, what it does, does not teach a relationship to any specific disease or establish any involvement of the polynucleotide in the etiology of any specific disease or teach which fragments might be active and would function as contemplated. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed nucleic acids thus the invention as claimed does not have a substantial utility. Because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

The rejection can be obviated by amending the claims to (a) delete reference in claims 18 and 19 to SEQ ID Nos 3 and 5 or nucleic acids encoding said sequences, (b) in claim 25 to delete combinations other than those reciting the sequence encoding amino acids 580-998 of SEQ ID NO:2 or their complete complement, (c) in claim 26 to delete reference to claims 19, 22, 24 and 25 and (d) cancel claims 21, 22.

***Claim Rejections - 35 USC § 112***

6. Claims 18 and 19 as drawn to SEQ ID Nos 3 and 5, claim 25 as drawn to all combinations other than sequences encoding amino acids 580-998 of SEQ ID NO:2 or their complete complement, claim 26 as drawn to claims 19, 22, 24 and 25 and claims 21-22 are rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by a specific utility, awell established utility or a substantial utility for the reasons set forth in the rejection

under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

7. Claims 1, 16, 19, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth a polynucleotide encoding SEQ ID Nos 2, 3, 5, 11 and 12 and therefore the written description is not commensurate in scope with the claims which as broadly written, and as defined in the specification, claim an isolated, enriched or purified nucleic acid molecule which reads on the natural gene encoding said sequences.

*Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is

achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The genes encoding the claimed polypeptides would be expected to have both introns and exons as well as regulatory elements. The specification teaches that "isolated" as drawn to nucleic acid includes DNA that is isolated from a natural source and specifically makes a distinction between natural DNA and cDNA (p. 7) and exemplifies the production of cDNAs corresponding to SEQ ID Nos 2, 3, 5, 11 and 12 and methods of isolating said sequences (see examples). Thus, the structure of the genes encoding the claimed SEQ ID Nos are not defined because it is not possible to work backward from the cDNA to derive a gene. With the exception of SEQ ID Nos 2, 3, 5, 11 and 12 (which would instantly allow the skilled artisan to envision the encoding cDNA), the skilled artisan cannot envision the detailed structure of the encompassed encoding polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25

USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Support for a gene is provided in the specification on page 7 wherein the nucleic acid of the invention is a natural DNA, which reads on a gene encoding a gene product. However, no disclosure, beyond the mere mention of a natural DNA is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only an isolated polynucleotide comprising SEQ ID Nos 2, 3, 5, 11 and 12, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

The rejection can be obviated by amending the claims to recite, for example, a recombinant nucleic acid.

8. Claim 26 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 is indefinite because it is dependent upon canceled claim 17. The rejection can be obviated by amending claim 26 to delete reference to claim 17.

Claim 18 is indefinite because it recites the phrase "comprising a nucleic acid". The claim is confusing because it is not clear whether, for example a nucleic acid comprising a single codon in common with SEQ ID NO:4 or 6 is being claimed or

whether the entire nucleic acid sequence of SEQ ID NO:4 or SEQ ID NO:6 is being claimed.

The rejection can be obviated by amending claim 18 to conform with the definite language recited in claim 16, that is "comprising the nucleic acid sequence"

***Claim Rejections - 35 USC § 102***

9. Claim 18 is rejected under 35 USC 102(b) as being anticipated by WO9300425, of record.

Due to the indefinite nature of the claim language, it is assumed for examination purposes that claim 18 is drawn to **a** (emphasis added) nucleic acid sequence of SEQ ID NO:4 or SEQ ID NO:6.

The claim is drawn to a nucleic acid sequence comprising a nucleic acid sequence of SEQ ID NO:4 or SEQ ID NO:6.

WO9300425 teaches a nucleic acid which comprises a codon TGG that is recited in both SEQ ID NO:4 and in SEQ ID NO:6 which encodes a tryptophan reside found in the encoded proteins. All of the limitations of the claim are met. The rejection can be obviated by amending claim 18 to replace "a" with the term "the".

10. Claims 3, 4 and 24 are allowable and free of the art.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
September 26, 2000